(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 December 2001 (06.12.2001)

PCT

(10) International Publication Number
WO 01/92303 A2

(51) International Patent Classification[7]: C07K 14/00

(21) International Application Number: PCT/US01/16967

(22) International Filing Date: 25 May 2001 (25.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/207,152 26 May 2000 (26.05.2000) US
60/207,257 26 May 2000 (26.05.2000) US
60/207,119 26 May 2000 (26.05.2000) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HUMAN ION CHANNELS

(57) **Abstract:** The present invention provides novel ion channel polypeptides and polynucleotides that identify and encode them. In addition, the invention provides expression vectors, host cells and methods for their production. The invention also provides methods for the identification of ion channel agonists/antagonists, useful for the treatment of human diseases and conditions.

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HUMAN ION CHANNELS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority of: Application Serial No. 60/207,152, filed 2000 May 26; Application Serial No. 60/207,257, filed 2000 May 26; and Application Serial No. 60/207,119, filed 2000 May 26; each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention is directed, in part, to nucleic acid molecules encoding ion channels, the novel polypeptides of these human ion channels, and assays for screening compounds that bind to these polypeptides and/or modulate their activities.

BACKGROUND OF THE INVENTION

[0003] Ion channels are "molecular gates" that regulate the flow of ions into and out of cells. Ion flow plays an important role in all brain cell communication necessary for learning and memory. Additionally, ion flow is important in many physiological processes including, but not limited to, heart rate and body movement. Aberrations in ion channels have been implicated in, amongst other disorders, epilepsy, schizophrenia, Alzheimer's disease, migraine, arrhythmia, diabetes, and stroke damage. Ions flow down their electrochemical gradient through the ion channels (passive transport). The core of the channel is hydrophilic, and contains a part of the protein, the selectivity filter, which recognizes only certain ions and allows them to pass through. Channels are named by the ion(s) they allow to pass. Examples of ion channels include, but are not limited to, calcium

channels, potassium channels, sodium channels, chloride channels, *etc*. An additional component of the channel is the gate. Only when the gate is open can the ions recognized by the selectivity filter pass through the channel. Gates open in response to a variety of stimuli, including, but not limited to, changes in membrane potential or the presence of certain chemicals outside or inside the cell. Channel names often also include an indication of what controls the gate: *e.g.*, "voltage-gated calcium channel." Presently, more than 50 different types of ion channels have been identified.

[0004] Communication between neurons is achieved by the release of neurotransmitters into the synapse. These neurotransmitters then activate receptors on the post-synaptic neuron. Many such receptors contain pores to rapidly conduct ions, such as sodium, calcium, potassium, and chloride, into the neuron. These pores, or channels, are made of protein subunits that are members of the family of proteins generally referred to as neurotransmitter-gated ion channel proteins. Included in this family are the serotonin 5-HT3 receptor, the gamma-aminobutyric-acid (GABA) receptor subunits, including gamma-1, rho-3, and beta-like, and the acetylcholine receptor protein subunits, including alpha-9 chain, epsilon chain, and beta-2 chain.

[0005] The neurotransmitter-gated ion channel superfamily includes 5-HT3, $GABA_A$, glutamate, glycine, and nicotinic acetylcholine receptor families. Within this superfamily, functional receptors are formed by homo- or heteropentamers of subunits having four transmembrane domains and an extracellular ligand-binding domain. The transmembrane domains of these receptors contribute to the formation of an ion pore.

[0006] Serotonin, also known as 5-hydroxytryptamine or 5-HT, is a biogenic amine that functions as a neurotransmitter, a mitogen and a hormone (Conley (1995) The Ion Channels FactsBook Vol. I. Extracellular Ligand-Gated Channels, Academic Press, London and San Diego. pp. 426). Serotonin activates a large number of receptors, most of which are coupled to activation of G-proteins. However, 5-HT3 receptors are structurally distinct and belong to the neurotransmitter-gated ion channel superfamily. 5-HT3 receptors are expressed both pre- and post-synaptically on central and peripheral neurons. Post-synaptic 5-HT3 receptors achieve their effects by inducing excitatory potentials in the post-synaptic neuron, whereas pre-synaptic 5-HT3 receptors modulate the release of other neurotransmitters from the pre-synaptic neuron (Conley, 1995). 5-HT3 receptors have important roles in pain reception, cognition, cranial motor neuron activity, sensory processing and modulation of

affect (Conley, 1995). Thus, ligands or drugs that modulate 5-HT3 receptors may be useful in treating pain, neuropathies, migraine, cognitive disorders, learning and memory deficits, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, emesis, cranial neuropathies, sensory deficits, anxiety, depression, schizophrenia, and other affective disorders.

[0007] Nicotinic acetylcholine receptors (AChR) are distinguished from other acetylcholine receptors by their affinity for nicotine and their structure—homo- or hetero-pentamers like all members of the neurotransmitter-gated ion channel superfamily. Nicotinic AChRs are found at the neuromuscular junction on skeletal muscle and on peripheral and central neurons. These receptors form nonselective cation channels and therefore induce excitatory currents when activated. Nicotinic AChRs are receptors for anesthetics, sedatives, and hallucinogens (Conley, 1995), and certain ligands have shown improvements in learning and memory in animals (Levin *et al.*, Behavioral Pharmacology, 1999, 10:675-780). Thus, ligands or drugs that modulate nicotinic AChRs could be useful for anesthesia, sedation, improving learning and memory, improving cognition, schizophrenia, anxiety, depression, attention deficit hyperactivity disorder, and addiction or smoking cessation. Expression of AChR subunits is regulated during development enabling the design of ligands or drugs specifically targeted for particular developmental stages or diseases.

[0008] The neurotransmitter γ-aminobutyric acid (GABA) activates a family of neurotransmitter-gated ion channels ($GABA_A$) and a family of G protein-coupled receptors ($GABA_B$) (Conley, 1995). $GABA_A$ receptors form chloride channels that induce inhibitory or hyperpolarizing currents when stimulated by GABA or $GABA_A$ receptor agonists (Conley, 1995). $GABA_A$ receptors are modulated by benzodiazepines, barbiturates, picrotoxin, and bicucuilline (Conley, 1995). Thus, ligands or drugs that modulate $GABA_A$ receptors could be useful in sedation, anxiety, epilepsy, seizures, alcohol addiction or withdrawal, panic disorders, pre-menstrual syndrome, migraine, and other diseases characterized by hyper-excitability of central or peripheral neurons. The pharmacology of $GABA_A$ receptors is affected by changing the subunit composition of the receptor. GABA receptor rho subunits are relatively specifically expressed in the retina (Cutting *et al.*, 1991, Proc. Natl. Acad. Sci. USA, 88:2673-7), and the pharmacology of rho receptor homomultimers resembles that of so-called $GABA_C$ receptors (Shimada *et al.*, 1992, Mol. Pharmacol. 41:683-7). Therefore,

GABA receptors consisting of rho subunits may be useful targets for discovering ligands or drugs to treat visual defects, macular degeneration, glaucoma, and other retinal disorders.

[0009] Potassium channels are proteins that form a pore allowing potassium ions to pass into or out of a cell. Potassium channels are comprised of an alpha- (or pore-forming) subunit, and are often associated with a beta- subunit. Three types of potassium ion pore-forming alpha-subunits have been described, exemplified by the *Shaker* channel (Jan, LY and Jan, YN. Voltage-gated and inwardly-rectifying potassium channels. J. Physiol. London 1997; 505:267-282), the inward-rectifier (ibid), and the two-pore (Fink M., Duprat, F., Lesage, F., Reyes, R., Romey, G., Heurteaux, C. and Lazdunski, M. Cloning, functional expression and brain localization of a novel outward rectifier K channel. EMBO J. 1996; 15:6854) channels. There are at least several members in each of these pore-forming families. These pores are comprised of a characteristic number of transmembrane-spanning domains; six transmembrane-spanning domains (*Shaker*), four transmembrane-spanning domains (two-pore) or two transmembrane-spanning domains (inward rectifier). Transmembrane-spanning domains are regions of the protein that traverse the plasma membrane of the cell. Hence, potassium channels with a *Shaker*-type alpha subunit are sometimes referred to as 6Tm-1P (for 6 transmembrane-spanning domains-1 pore), inward-rectifier channels as 2Tm-1P and two-pore channels as 4Tm-2P.

[00010] The 4Tm-2P family of potassium channels was initially discovered in the nematode *C. elegans* (Salkoff, L. and Jegla, T. 1995,Neuron, 15: 489), but have also been found in yeast, *Drosophila melanogaster*, bacteria, plants and mammalian cells (Lesage F and Lazdunski M. (1999). "Potassium Ion Channels, Molecular Structure, Function, and Diseases" in Current Topics in Membranes 46; 199-222 ed. Kurachi, Y., Jan, LY., and Lazdunski, M.). In addition to the different biophysical characteristics described above the 4Tm-2P family of potassium channels have different physiological characteristics as well. For example they are regulated by H^+ ions, extracellular K^+ and Na^+ ions, and also by protein kinase c and protein kinase a activators. 4Tm-2P potassium channels are time and voltage-independent, and thus remain open at all membrane potentials. Because of this, these potassium channels are postulated to be responsible for the background potassium ion currents that are thought to set the resting membrane potential (Lesage *et al.*, (1999), "Potassium Ion Channels, Molecular Structure, Function, and Diseases" in Current Topics in Membranes 46; 199-222 ed. Kurachi, Y., Jan, LY., and Lazdunski, M.).

[00011] Potential uses for the channels described herein include the discovery of agents that modify the activity of the channels. Two previously described members of this family (TASK and TREK-1) are activated by volatile general anesthetics such as chloroform halothane and isoflurane (Patel *et al.*, Nature Neuroscience, 1999, 2:422-426), implicating these channels as a site of activity for these anesthetics. In addition, compounds that modify the activity of these channels may also be useful for the control of neuromotor diseases including epilepsy and neurodegenerative diseases including Parkinson's and Alzheimer's. Also compounds that modulate the activity of these channels may treat diseases including but not limited to cardiovascular arrhythmias, stroke, and endocrine and muscular disorders.

[00012] Therefore, ion channels may be useful targets for discovering ligands or drugs to treat many diverse disorders and defects, including schizophrenia, depression, anxiety, attention deficit hyperactivity disorder, migraine, stroke, ischemia, and neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, glaucoma and macular degeneration. In addition compounds which modulate ion channels can be used for the treatment of cardiovascular diseases including ischemia, congestive heart failure, arrhythmia, high blood pressure and restenosis.

SUMMARY OF THE INVENTION

[00013] The present invention relates to an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to a sequence selected from the group consisting of SEQ ID NO:20 to SEQ ID NO:38, or a fragment thereof. The nucleic acid molecule encodes at least a portion of ion-x (where x is 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, and 175). In some embodiments, the nucleic acid molecule comprises a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:20 to SEQ ID NO:38, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, and fragments thereof.

[00014] According to some embodiments, the present invention provides vectors which comprise the nucleic acid molecule of the invention. In some embodiments, the vector is an expression vector.

[00015] According to some embodiments, the present invention provides host cells which comprise the vectors of the invention. In some embodiments, the host cells comprise expression vectors.

[00016] The present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, said portion comprising at least 10 nucleotides.

[00017] The present invention provides a method of producing a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:20 to SEQ ID NO:38,or a homolog or fragment thereof. The method comprising the steps of introducing a recombinant expression vector that includes a nucleotide sequence that encodes the polypeptide into a compatible host cell, growing the host cell under conditions for expression of the polypeptide and recovering the polypeptide.

[00018] The present invention provides an isolated antibody which binds to an epitope on a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:20 to SEQ ID NO:38,or a homolog or fragment thereof.

[00019] The present invention provides an method of inducing an immune response in a mammal against a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:20 to SEQ ID NO:38, or a homolog or fragment thereof. The method comprises administering to a mammal an amount of the polypeptide sufficient to induce said immune response.

[00020] The present invention provides a method for identifying a compound which binds ion-x. The method comprises the steps of: contacting ion-x with a compound and determining whether the compound binds ion-x. Compounds identified as binding ion-x may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

[00021] The present invention provides a method for identifying a compound which binds a nucleic acid molecule encoding ion-x. The method comprises the steps of contacting

said nucleic acid molecule encoding ion-x with a compound and determining whether said compound binds said nucleic acid molecule.

[00022] The present invention provides a method for identifying a compound that modulates the activity of ion-x. The method comprises the steps of contacting ion-x with a compound and determining whether ion-x activity has been modulated. Compounds identified as modulating ion-x activity may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

[00023] The present invention provides a method of identifying an animal homolog of ion-x. The method comprises the steps screening a nucleic acid database of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, or portion thereof.

[00024] The present invention provides a method of identifying an animal homolog of ion-x. The methods comprises the steps screening a nucleic acid library of the animal with a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, or a portion thereof; and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:19, or a portion thereof.

[00025] Another aspect of the present invention relates to methods of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor. The methods comprise the steps of assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one ion channel that is expressed in the brain. The ion channels comprise an amino acid sequence selected from the group consisting of: SEQ ID NO:20 to SEQ ID NO:38, and allelic variants thereof. A diagnosis of the disorder or predisposition is made from the presence or absence of the mutation. The presence of a mutation altering the amino acid sequence, expression, or biological activity of the ion channel in the nudeic acid correlates with an increased risk of developing the disorder.

[00026] The present invention further relates to methods of screening for an ion-x mental disorder genotype in a human patient. The methods comprise the steps of providing a biological sample comprising nucleic acid from the patient, in which the nucleic acid includes

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Ile Phe Phe Ala Leu Val Gly Ile Pro Leu Asn Leu Val Val Leu Asn
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Arg Leu Gly His Leu Met Gln Gln Gly Val Asn His
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Ile Ser Cys Ala Ala Ala Ile Leu Pro Phe Trp Glu Thr Gln Leu Asp
1 5 10 15

Phe Glu Asn Ala Phe Tyr Phe Cys Phe Val Thr Leu Thr Thr Ile Gly
20 25 30

Phe Gly Asp Thr Val Leu Glu His Pro Asn Phe Phe Leu Phe Phe Ser
35 40 45

Ile Tyr Ile Ile Val Gly Met
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